IgE-Mediated Cytokine Storm in Vaccinated Populations: Call for Further Investigation and Caution

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ABSTRACT

Emerging evidence suggests that cytokine storms following vaccination for respiratory viruses, such as COVID-19 and influenza, may involve IgE-mediated hypersensitivity. This hyperinflammatory reaction, characterized by massive cytokine release and severe tissue damage, is hypothesized to be driven by mast cell degranulation and histamine release. Mast cell stabilizers and histamine blockers, such as cromolyn sodium, may be of therapeutic benefit. Suspension of respiratory virus vaccination should be considered while this mechanism and potential therapy are investigated. Comprehensive immune profiling, including markers like IgE, histamine, and tryptase, could identify individuals at risk for severe reactions.

Case Report

A 45-year-old Caucasian female physician with a history of food and latex allergies received an influenza vaccination on Oct 2, 2012, administered by employee health services. The nurse did not inquire about her allergies or medical history. Post injection, the patient experienced symptoms including flushing, dizziness, and nasal congestion. It was subsequently found that the vaccine contained natural rubber latex, contraindicated for individuals with latex allergies.

The patient self-administered 50 mg of diphenhydramine and returned home. Throughout the evening, she experienced worsening shortness of breath, presyncope, throat swelling, and hoarseness. The following morning, nursing staff at her workplace observed facial edema and transported her to the emergency room, where she was treated for anaphylaxis with intravenous diphenhydramine and steroids and then discharged.

Subsequent episodes occurred after meals and exposure to latex products, including multiple instances of presyncope accompanied by shortness of breath. Approximately two weeks later, while working in the operating room, skin contact with natural rubber latex led to hives, facial swelling, and progressive shortness of breath, necessitating another emergency room visit and treatment with epinephrine and intravenous diphenhydramine.

Over the ensuing weeks, the patient frequently consulted her primary care clinician due to worsening facial edema, hoarseness, presyncope, and syncope, prompting increased doses of prednisone, diphenhydramine, cetirizine, ranitidine, and montelukast. Persistent episodes led to frequent emergency room visits, some requiring administration of epinephrine. One hospital admission involved three days of intravenous steroids to address persistent shortness of breath, hoarseness, and facial and subcutaneous edema.

Laboratory evaluations consistently showed eosinophilia and elevated total IgE levels specific to latex. A local allergist noted the relationship between both food and latex exposures triggering reactions. Full laboratory evaluation of IgE specific to common foods revealed positive results for all fruits, vegetables (except peas), and grains, but negative results for meat, eggs, milk, coffee, and chocolate.

At this stage, the patient was taking prednisone 60 mg twice daily, diphenhydramine 50 mg twice daily, cetirizine 20 mg twice daily, montelukast 10 mg once daily, ranitidine 10 mg twice daily, and utilizing an albuterol inhaler every 4-6 hours as needed. However, she continued to experience facial edema, hoarseness, shortness of breath, syncope, near syncope, and a general sense of impending doom, leading to multiple ambulance calls and emergency room visits.

Evaluation at Johns Hopkins by a pediatric allergist resulted in immediate initiation of liquid cromolyn sodium 200 mg (2 ampules) orally one-half hour before meals and at bedtime and removal of all IgE-positive foods from the patient's diet, which was restricted to a list of 20 safe foods. Goals included reducing other medications, eliminating ambulance calls and emergency room visits, and discontinuing epinephrine use.

The patient strictly adhered to the diet and avoided all latex exposures. After two to three months, the frequency of allergic reactions decreased, allowing for tapering and eventual discontinuation of other medications over one year. Food reintroduction began with vegetables genetically dissimilar from the latex-fruit syndrome category under strict protocols. The patient's office, surgical centers, and hospitals where she both worked and sought medical care implemented latex-safe protocols, ensuring all medical and office equipment were latex-free. Latex-containing medications posed challenges due to a lack of labeling, necessitating communication with manufacturers.

After three years, it was decided to try to wean her off cromolyn sodium. This occurred over nearly another year, with fear of allergic reactions acting as a limiting factor. No new foods were introduced during this period. After cromolyn sodium was discontinued, foods were slowly re-introduced under strict protocols, with continued strict avoidance of latex. The patient had no significant allergic reactions, and therefore in 2020 more foods were added, including grains beyond quinoa and many fruits and vegetables. As of the writing of this report, the patient can consume 90 percent of previously allergenic foods, although kiwi, avocado, walnut, and banana are still avoided due to concern about the latex-fruit syndrome.

The patient continues to avoid latex exposures. A recent inadvertent exposure caused a delayed type II rash without systemic symptoms, which was resolved with cortisone cream. The patient is currently medication free.

This patient experienced her first anaphylactic reaction at age three, leading to hospitalization and identification of

allergies to chocolate, tomatoes, oranges, and environmental factors, followed by strict avoidance and gradual reintroduction. She was involved in a major car accident in 1980, resulting in a ten-hour reconstructive leg surgery involving latex gloves. During her surgical internship in the 1990s, she developed topical latex glove allergies, exacerbated after childbirth in 1995 with latex glove use, and worsened by root canal surgery involving natural rubber latex. The latex-containing influenza vaccination induced anaphylaxis and exacerbated latex fruit syndrome and cross-reactive food allergies, with frequently recurring life-threatening consequences.

Cromolyn sodium stabilized mast cells, contributing to stabilization and remission of recurrent anaphylaxis.

IgE-Mediated Cytokine Storms

Cytokine storms are hyperinflammatory reactions involving massive cytokine release, often resulting in severe tissue damage. Research indicates that IgE-mediated hypersensitivity could play a significant role in these reactions, particularly following respiratory virus vaccinations.[1] This pathway, typically associated with mast cell degranulation and histamine release, may be triggered in sensitized individuals upon exposure to similar viral antigens. Historical insights on anaphylaxis, such as those described by Charles Richet in his 1913 Nobel lecture, underscore that unnatural antigen exposures via injections, especially through repeated exposures, can lead to severe allergic responses and anaphylactic reactions.[2]

The similarity between allergic reactions triggered by influenza vaccination and dengue fever provides a useful analogy. For instance, repeated influenza vaccination has led to increased IgE responses, potentially triggering severe allergic reactions similar to dengue shock syndrome, in which IgE-mediated responses upon re-exposure lead to escalating inflammation and, in severe cases, shock.[3] Specific studies have demonstrated production of IgE anti-Influenza virus antibodies in the vaccinated.[4] Such parallels support the hypothesis that repeated vaccine exposure could heighten immune sensitivity and drive cytokine storms upon subsequent viral exposure. Recent studies have demonstrated mechanisms underlying cytokine release and allergic reactions associated with COVID-19 mRNA-LNP vaccines and discussed relevant preventive measures and treatments.[1,5,6] Some COVID-19 patients experiencing cytokine storms have shown symptomatic improvement with allergy medications, particularly during the peak inflammatory phases. Filcek et al. demonstrated promising results in mitigating severe symptoms by addressing IgE-mediated pathways directly.[6] This aligns with the hypothesis that IgE responses contribute to severe immune reactions in vaccinated individuals and suggests that cromolyn sodium in addition to other medications such as antihistamines and corticosteroids that address the IgE-mediated component of the cytokine storm should be part of the treatment regimen for managing these patients.

Cromolyn sodium, which is is available in oral and inhaled forms, is a mast cell stabilizer that prevents the subsequent release of inflammatory mediators through mast cell degranulation. This includes both histamine and leukotrienes that cause allergic symptoms and bronchoconstriction. Cromolyn sodium is different from typical antihistamine medications, which reduce the action of histamines following the release from mast cells.[7]

Corticosteroids are effective clinically because they block many of the inflammatory pathways that are abnormally activated in allergic processes. Cromolyn sodium inhibits immediate and late reactions.[7]

The typical initial dose of cromolyn sodium is 200 mg (2 ampules) orally one-half hour before meals and at bedtime. If satisfactory control is not achieved within 2 to 3 weeks, the dose can be increased. The dose can be reduced to the minimum required to maintain adequate control once a therapeutic response has been achieved. The maximum dose is 40 mg/kg/day.

Cromolyn sodium is supplied in ampules (100 mg/5 mL). At time of use the patient breaks open ampule(s) and squeezes the contents into a 6-to-8 oz glass of water. It needs to be protected from light, so the vials/ampules are in foil pouches until ready to use. No evidence of tachyphylaxis to the beneficial effects has been reported. Review of the available literature has shown no contraindications to long-term use and no evidence of serious adverse events with either short- or long-term use.[7]

Cromolyn sodium is recommended for patients with blood tests or clinical evidence of IgE-mediated cytokine storm, either from complications of vaccine/biologic administration or viral illness. It can dramatically decrease histamine release and the cascade that ensues.[8-10]

Questions Regarding the Benefits and Risks of Vaccination against Respiratory Viruses

Potential adverse effects of vaccination are accepted if outweighed by benefits. But these are being regarded with skepticism. Even if influenza vaccination reduces cases of influenza, it may increase susceptibility to other respiratory viruses, including a reported 36% increase in coronavirus susceptibility.[11] Repeated antigen exposure from vaccination in consecutive years may intensify allergic responses and immune reactivity.[3]

Two decades ago, a study demonstrated that influenza vaccination lacked a clear impact on mortality, with the study's authors concluding the following: "We could not correlate increasing vaccination coverage after 1980 with declining mortality rates in any age group. Because fewer than 10% of all winter deaths were attributable to influenza in any season, we conclude that observational studies substantially overestimate vaccination benefit."[12] A study in 2008 analyzing the potential benefits of yearly influenza vaccinations in the elderly concluded the following: "The 51% reduction in mortality with vaccination initially observed in patients with pneumonia who did not have influenza was most likely a result of confounding. Previous observational studies may have overestimated mortality benefits of influenza vaccination."[13] The authors pointed out the paucity of adequate studies demonstrating statistically significant benefits and pointed out concerns that this public policy is substantially backed only by observational studies.[13] In 2006, an Italian study concluded the following: "After the late 1980s, no decline in age-adjusted excess mortality was associated with increasing influenza vaccination distribution primarily targeted for the elderly. These findings suggest that either the vaccine failed to protect the elderly against mortality

(possibly due to immune senescence), and/or the vaccination efforts did not adequately target the frailest elderly. As in the U.S., our study challenges current strategies to best protect the elderly against mortality, warranting the need for better controlled trials with alternative vaccination strategies."[14]

Following COVID-19 vaccination, fatal adverse effects were reported, and guidelines were suggested for improving causal investigation.[15] A systematic review of autopsy findings indicated heightened all-cause mortality in some individuals.[16, 17] This may reflect unintended consequences associated with vaccine-related immune responses and suggests a need to further explore underlying immunopathology. In a narrative review it has been shown that the SARS-CoV-2 spike protein, especially the S1 subunit, may be pathogenic. It was also found that widely biodistributed spike proteins create a wide variety of diseases. It concluded that the whole premise of gene-based vaccines producing foreign antigens in human tissues has elevated risks for autoimmune and inflammatory conditions.[18]

Further research is urgently needed to investigate:

- Longitudinal changes in IgE and other immune markers in vaccinated populations;
- The potential for cross-reactivity between influenza and coronavirus antigens, possibly exacerbating immune responses;
- Clinical trials to assess the effectiveness of allergy treatments, including cromolyn sodium and other stabilizers, for managing cytokine storms related to respiratory virus vaccinations;
- More adequate studies evaluating the effectiveness as well as risks and benefits of yearly influenza vaccination; and
- More adequate studies evaluating the effectiveness as well as risks and benefits of the mRNA biologic platform.

Conclusions

Suspension of respiratory virus vaccinations for at-risk populations is recommended until the IgE-mediated mechanisms can be further investigated. Implementing comprehensive immune profiling, including markers such as histamine, IgE, tryptase, and eosinophils, could help identify patients predisposed to severe inflammatory reactions. For those showing signs of cytokine storms, integrating allergy treatments, including histamine blockers and mast cell stabilizers like cromolyn sodium, may mitigate severe outcomes.

This suspension is especially important considering the paucity of adequate studies of benefits and risks of the current public health policy of recommending yearly influenza vaccinations and COVID boosters.

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REFERENCES

1. Awaya T, Hara H, Moroi M. Cytokine storms and anaphylaxis following COVID-19 mRNA-LNP vaccination: mechanisms and therapeutic approaches. *Diseases* 2024;12(10):231. Available at: https://www.mdpi.com/2980522. Accessed Feb 24, 2025.
2. Richet C. Nobel lecture, Dec 11, 1913. Available at: https://www.nobelprize.org/prizes/medicine/1913/richet/lecture/. Accessed May 11, 2025.
3. Arumugham V. Rapid Response: Influenza vaccines and dengue-like disease. *BMJ* 2018;360:k1378. Available at: https://www.bmj.com/content/360/bmj.k1378/rr-15. Accessed Feb 24, 2025.
4. Smith-Norowitz TA, Wong D, Kusonruksa M, et al. Long term persistence of IgE anti-influenza virus antibodies in pediatric and adult serum post vaccination with influenza virus vaccine. *Int J Med Sci* 2011;8(3):239-244. doi:10.7150/ijms.8.239. Available at: https://www.medsci.org/v08p0239.htm. Accessed Feb 24, 2025.
5. Arumugham V. Immunological mechanisms explaining the role of vaccines, IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines: predictions and confirmations. *SSRN*, Oct 17, 2020. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3722710. Accessed Feb 24, 2025.
6. Filcek M, Vats M, Skrzyniarz-Plutecka A. Discovery of the mechanism of COVID-19, SIRS and sepsis, defense and treatment: mast cells and histamine storm an overlooked aspects in COVID-19 and in ventilated patients: potential role of antihistamine. *J MAR Pulmonol* 2021;3(5). Available at: https://www.researchgate.net/publication/355038967_Discovery_of_the_Mechanism_of_COVID19_SIRS_and_SEPSIS_Defense_and_Treatment_Mast_cells_and_Histamine_Storm_an_Overlooked_Aspects_in_COVID-19_and_in_Ventilated_Patients_Potential_Role_of_Antihistamine. Accessed Feb 24, 2025.
7. Minutello K, Gupta V. Cromolyn Sodium (updated Oct 28, 2024). StatPearls [Internet]. Treasure Island, Fla.: StatPearls Publishing; January 2025 Available at: https://www.ncbi.nlm.nih.gov/books/NBK557473/. Accessed Feb 24, 2025.
8. Hafezi B, Chan L, Knapp JP, et al. Cytokine storm syndrome in SARS-CoV-2 infections: a functional role of mast cells. *Cells* 2021;10(7):1761. Available at: https://www.mdpi.com/1185722. Accessed Feb 24, 2025.
9. Yousefi H, Mashouri L, Okpechi SC, Alahari N, Alahari SK. Repurposing existing drugs for the treatment of COVID-19/SARS-CoV-2 infection: a review describing drug mechanisms of action. *Biochem Pharmacol* 2021;183:114296. Available at: https://www.sciencedirect.com/science/article/pii/S0006295220305323. Accessed Feb 24, 2025.
10. Malone RW, Tisdall P, Fremont-Smith P, et al. COVID-19: Famotidine, histamine, mast cells, and mechanisms. *Front Pharmacol* 2021;12:633680. Available at: https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.633680/full. Accessed Feb 24, 2025.
11. Wolff GG. Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017-2018 influenza season. *Vaccine* 2020;38(2):350-354. Available at: https://www.sciencedirect.com/science/article/pii/S0264410X19313647. Accessed Feb 24, 2025.
12. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med* 2005;165(3):265-272. Available at https://pubmed.ncbi.nlm.nih.gov/15710788/. Accessed Mar 15, 2025.
13. Eurich DT, Marrie TJ, Johnstone J, Majumdar SR. Mortality reduction with influenza vaccine in patients with pneumonia outside 'flu' season: pleiotropic benefits or residual confounding? *Am J Respir Crit Care Med* 2008;178(5):527-533. Available at: https://pubmed.ncbi.nlm.nih.gov/18556629/. Accessed Mar 15, 2025.
14. Rizzo C, Viboud C, Montomoli E, Simonsen L, Miller M. Influenza-related mortality in the Italian elderly: No decline associated with increasing vaccination coverage. *Vaccine* 2006;24(42-43):6468-6475. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0264410X0600764X?via%3Dihub%20. Accessed Mar 15, 2025.
15 Lii JT, Cai PK, Shau KL, et al. A systemic review and recommendation for an autopsy approach to death followed the COVID 19 vaccination. *Forensic Sci Int* 2022;340(November):111469. Available at: https://www.sciencedirect.com/science/article/pii/S0379073822002997. Accessed Feb 24, 2025.
16. Hulscher N, Hodkinson R, Makis W, McCullough PA. Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis. *ESC Heart Fail*, Jan 14, 2024. Available at: https://onlinelibrary.wiley.com/share/JEC2MMX6JQSS2V6KIEIJ?target=10.1002/ehf2.14680. Accessed Feb 24, 2025.
17. Alessandria M, Malatesta GM, Berrino F, Donzelli A. A critical analysis of all-cause deaths during COVID-19 vaccination in an Italian province. *Microorganisms* 2024;12(7):1343. Available at: https://www.mdpi.com/2852574. Accessed Feb 24, 2025.
18. Parry PI, Lefringhausen A, Turni C, et al. 'Spikeopathy': COVID-19 spike protein is pathogenic, from both virus and vaccine mRNA. *Biomedicines* Aug 17, 2023;11(8):2287. Available at: https://pubmed.ncbi.nlm.nih.gov/37626783/. Accessed Mar 15, 2025.